Plague

Epidemiology & Clinical Aspects
CDC clinical trial, Africa

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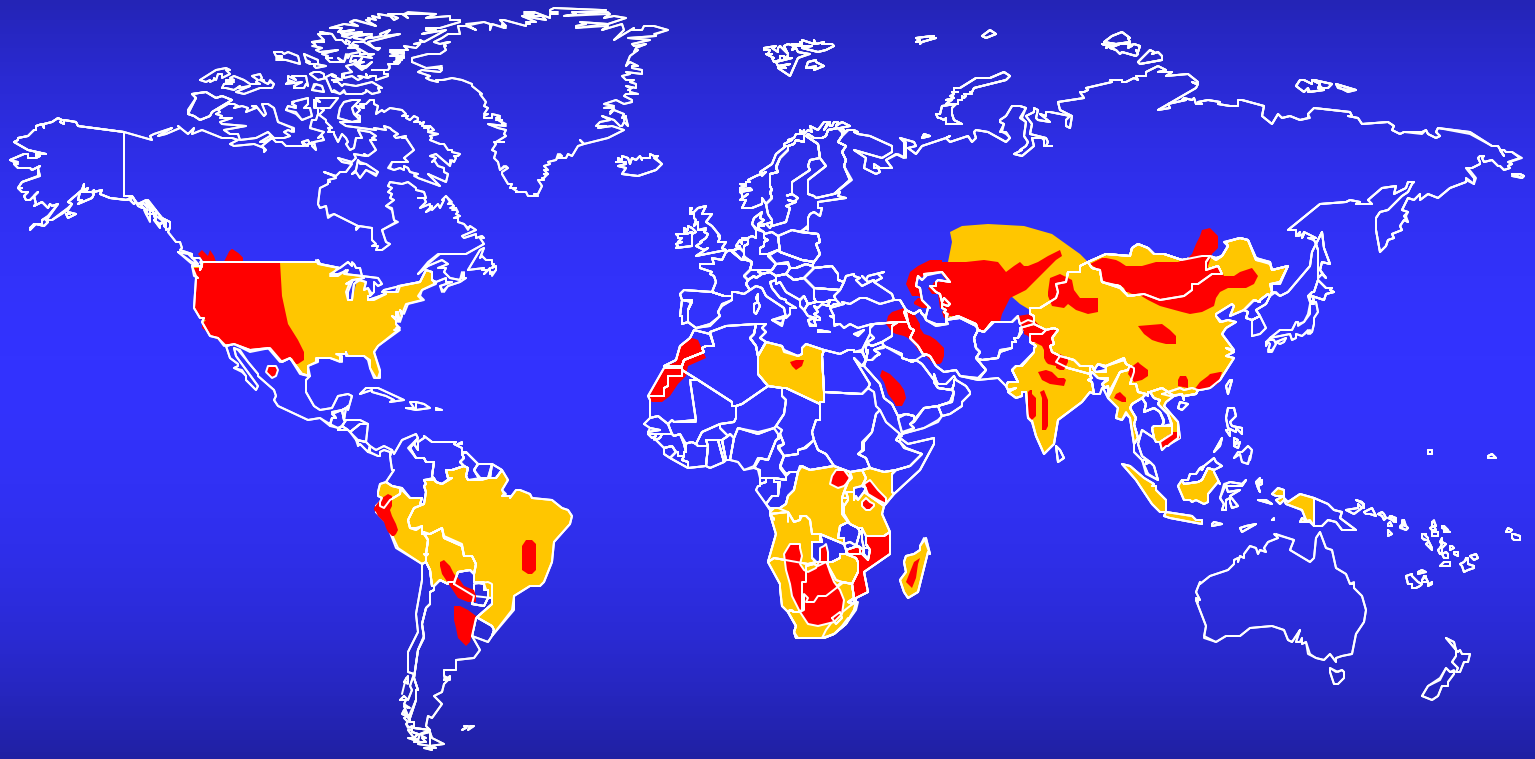
This Presentation

1. Epidemiology of plague
   - World
   - US
   - Bioterrorism
2. Clinical aspects of plague
   - Naturally occurring plague
   - Pneumonic plague
3. CDC clinical trial field sites in Uganda and Madagascar

Global Distribution of Plague



Countries reporting plague, 1970-2000

Probable Sylvatic foci

Compiled from WHO, CDC, and country sources

CDC
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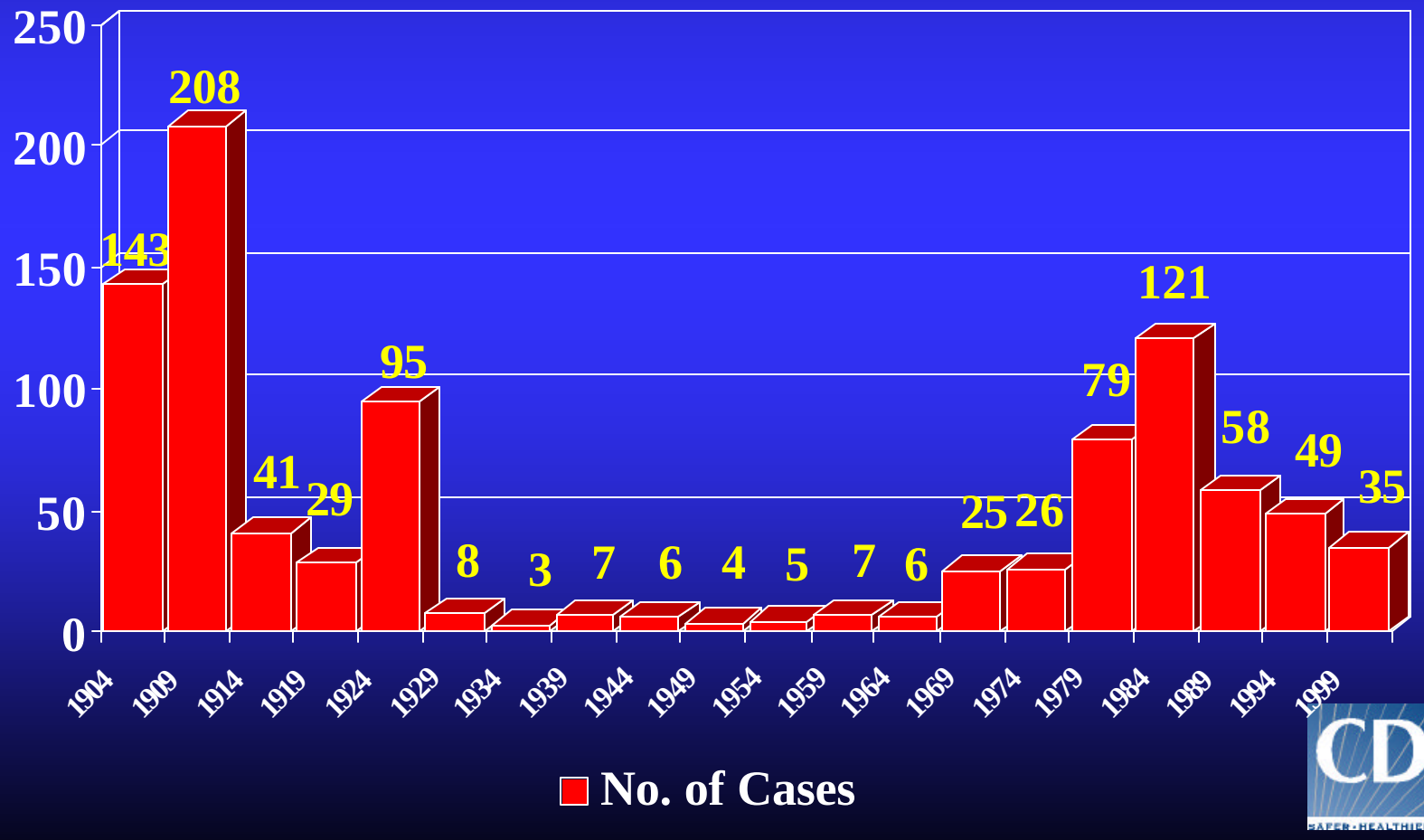
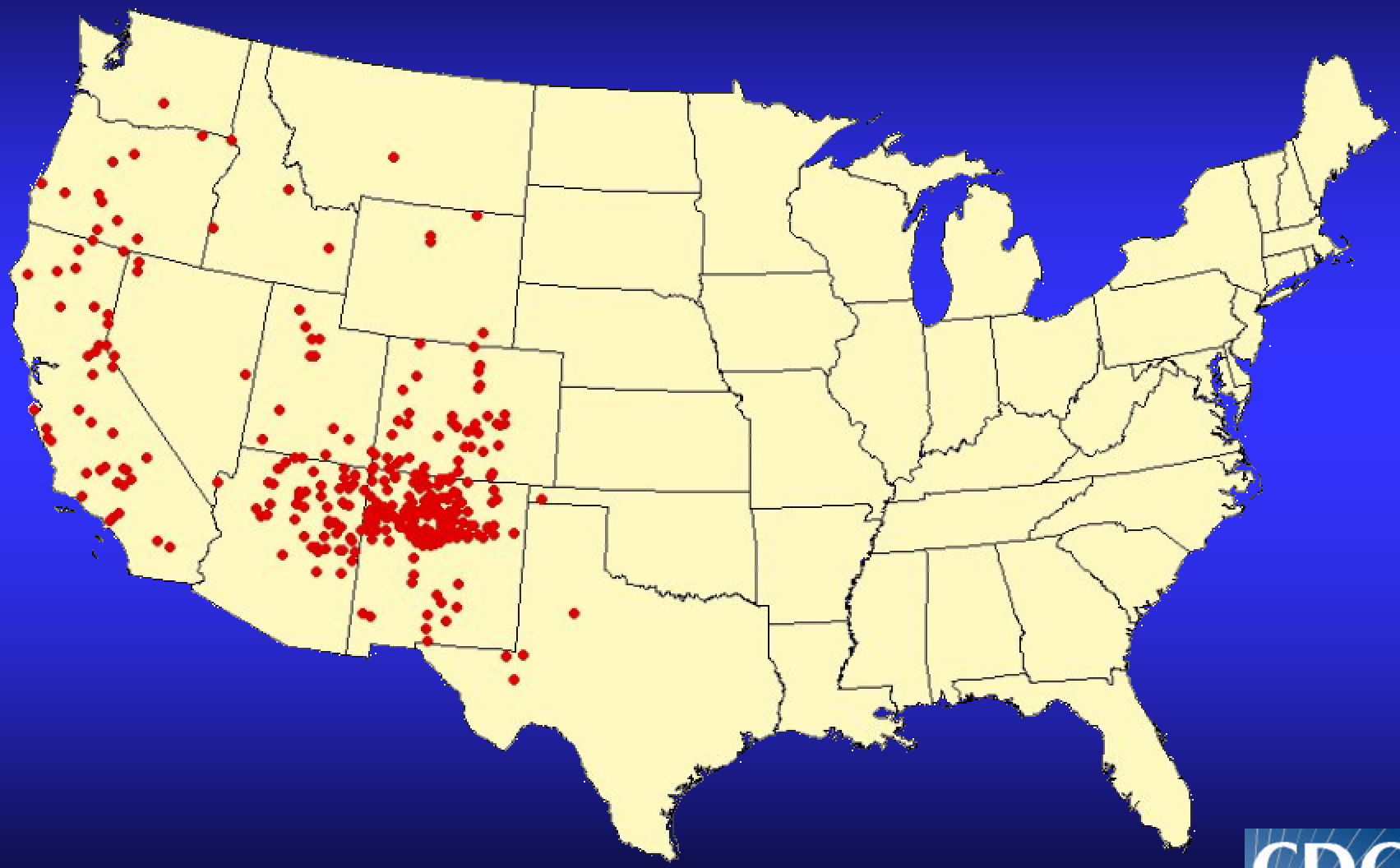
Reported Human Plague Cases By 5 Year-U.S.A., 1900-1999



Human Plague Cases Reported to CDC, 1970-2000



1 dot = 1 case, placed randomly within county of occurrence; N=375

CDC
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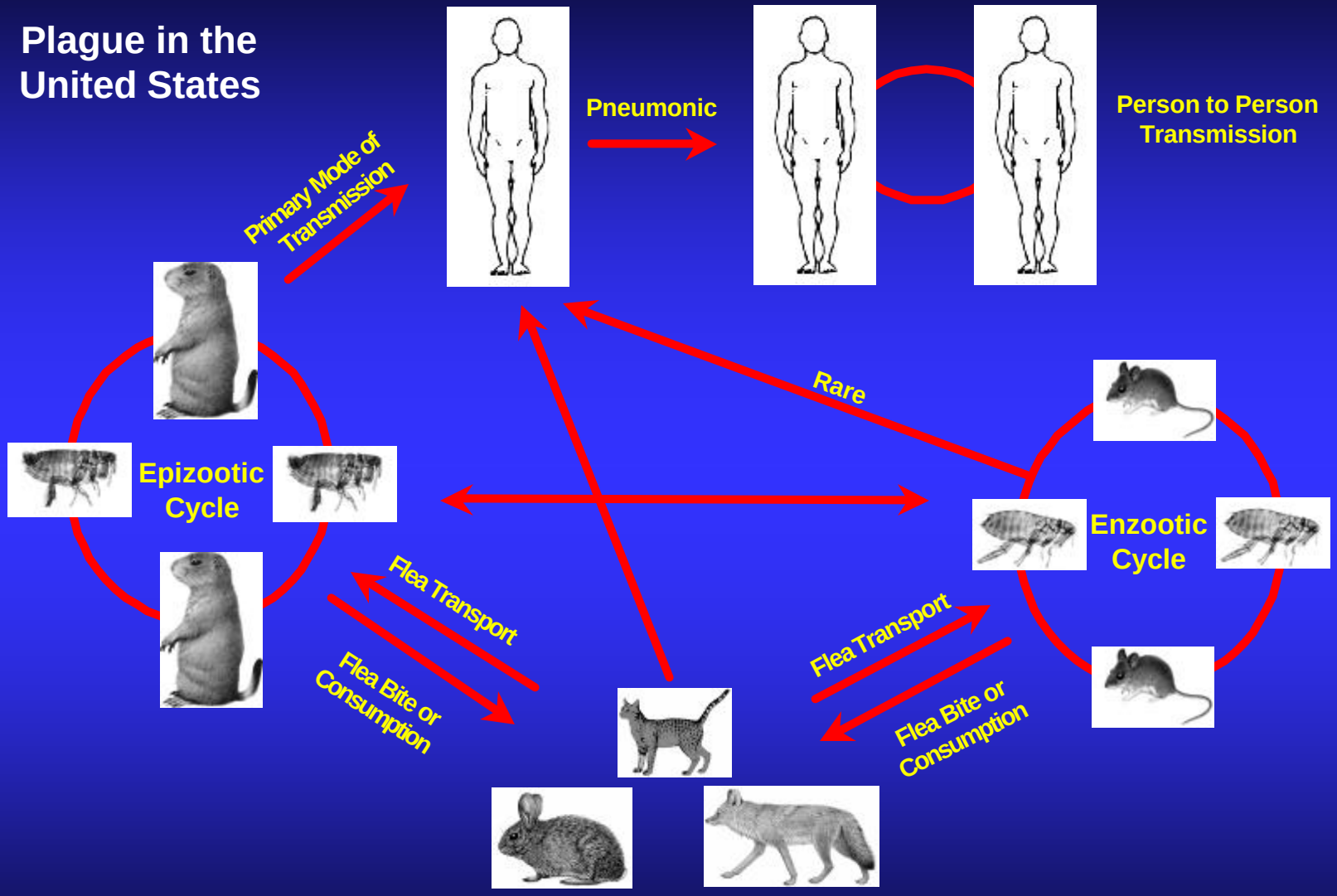
Plague in the United States



CDC
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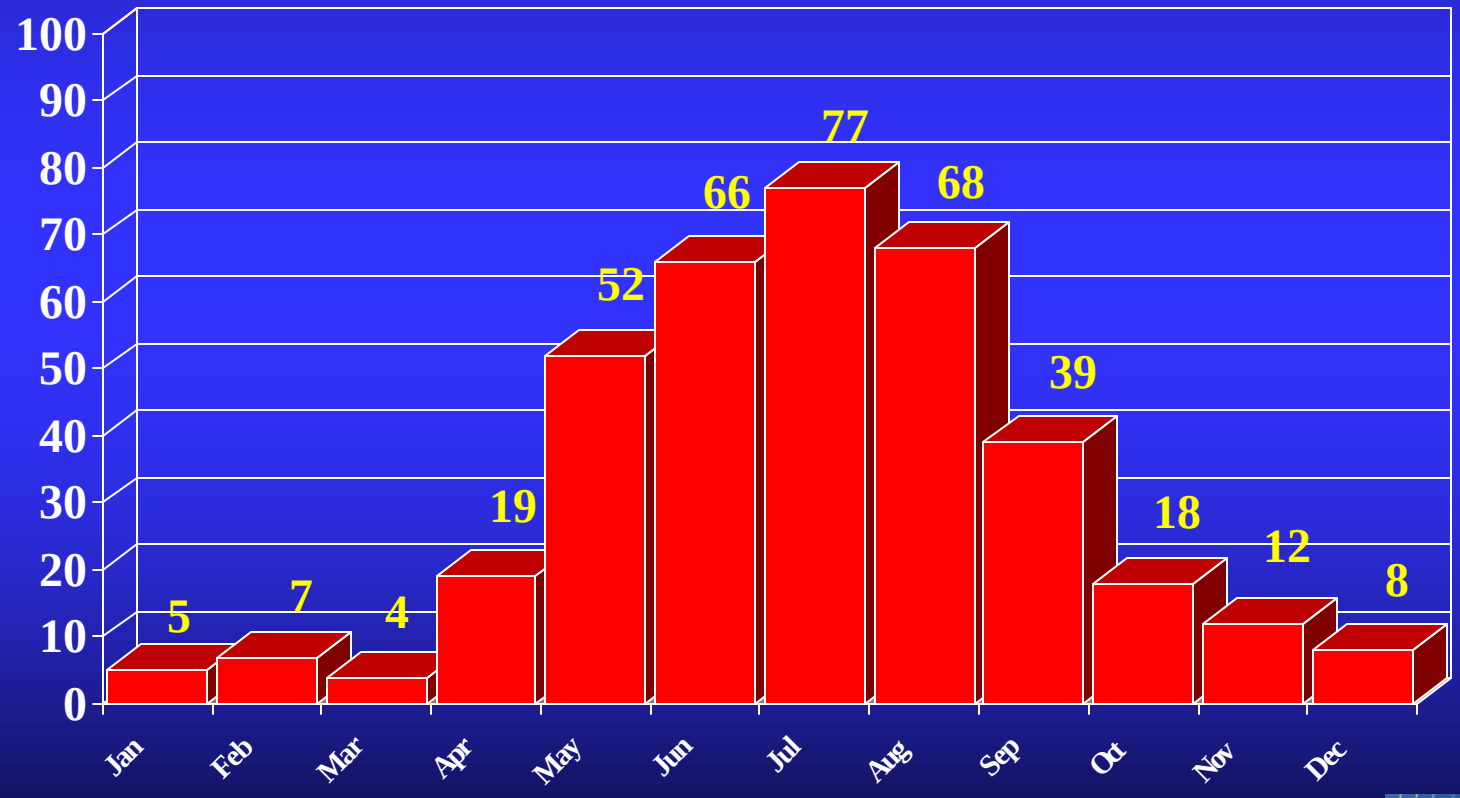
Cumulative Reported Human Plague Cases By Month of Onset, US, 1970 - 2002



N = 376

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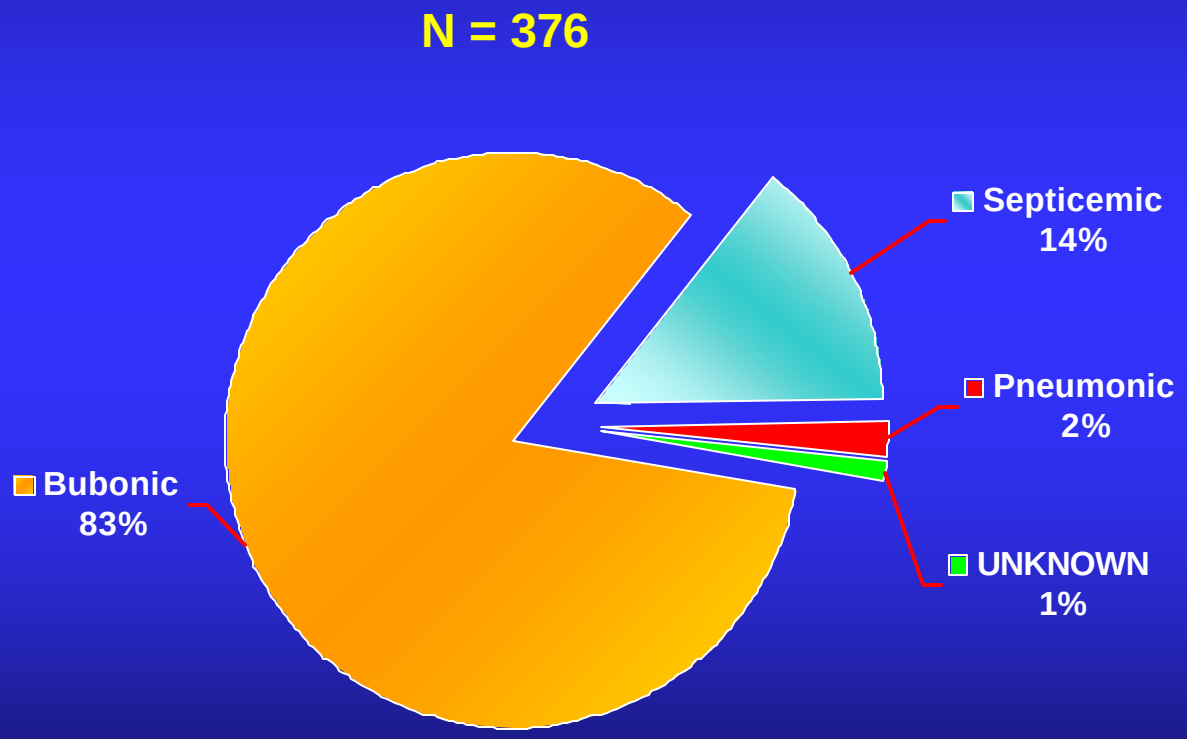
Plague in the U.S., 1970-2002

Primary Presentation



Bioweapon Potential of Plague

- *Yersinia pestis* weaponized by USSR for aerosol delivery
- Could be engineered for:
  - Antimicrobial resistance
  - Virulence
  - F1 deficiency
- Lyophilized formulations ?
- Threat from environmental contamination
- Secondary person-to-person transmission

WHO Modeling Scenario (1970)

- 50 kg over city of 5 million
  - 150,000 cases
  - 36,000 deaths
  - Hospitalization for 80,000-100,000
- Secondary spread
  - Up to 500,000 persons
  - 100,000 deaths

Pneumonic Plague

- Secondary PP: hematogenous spread from bubo or blood to the lungs
- Primary PP: direct infection of the lungs

Primary Pneumonic Plague

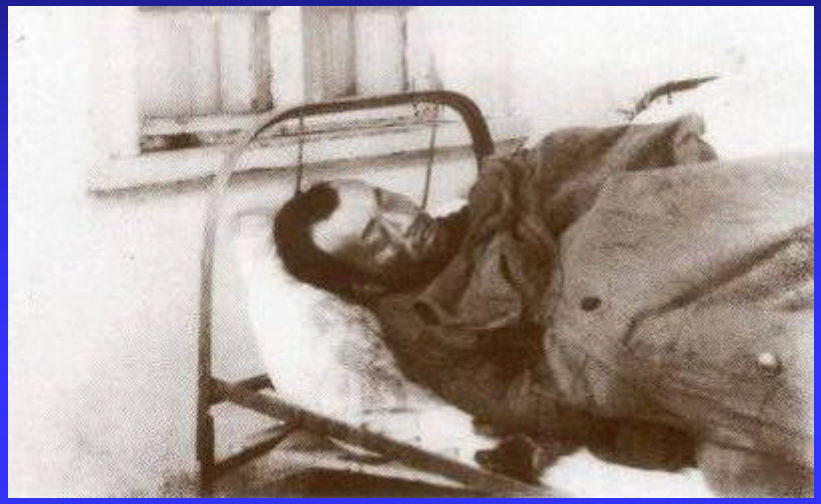
- Short incubation period (2-4 d, range 1-6 d)
- Acute, fulminating course (SIRS)
  - Intensive support required
- 100% mortality in 3-6 days if not treated early (< 20 hours)
- In USA
  - 2 outbreaks of PPP: 1919 and 1924
  - Since 1925, 8 cases of PPP, mostly from cats

Clinical stages of untreated primary pneumonic plague (1) *

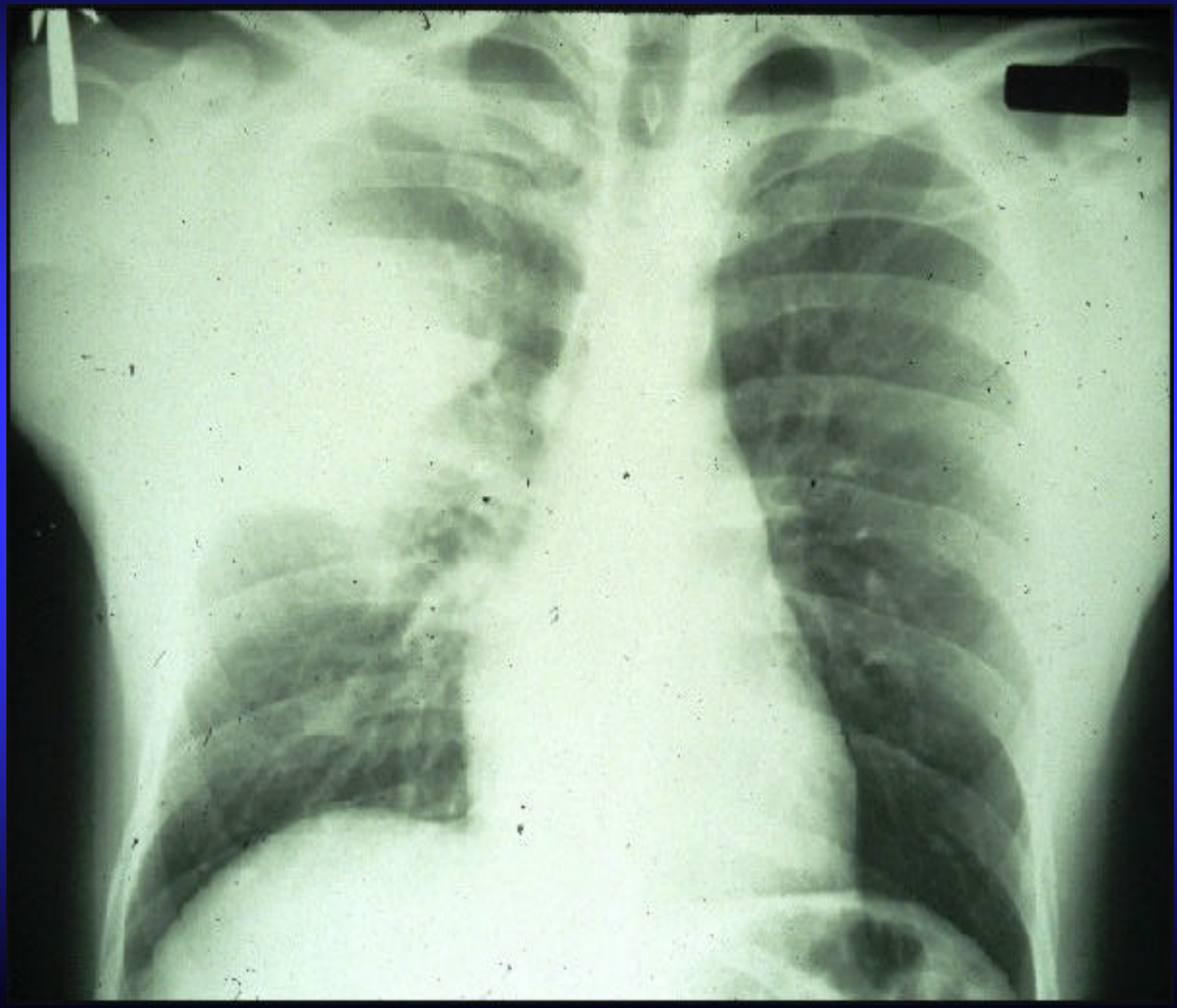
- Initial stage ("non-infectious stage"):
  (First several hours to 24 hours)
  - Sudden onset: malaise, chills, severe headache
  - Increased respiratory and heart rates
  - Temperature rises steadily
  - After several hours: dry cough, which becomes progressively productive
  - Very few plague bacilli in sputum
- Final stage:
  (One to few hours before death)
  - Bright red sputum
  - Many plague bacilli in almost pure culture

* Sources: Wu Lien-Teh, Pollitzer, Butler.

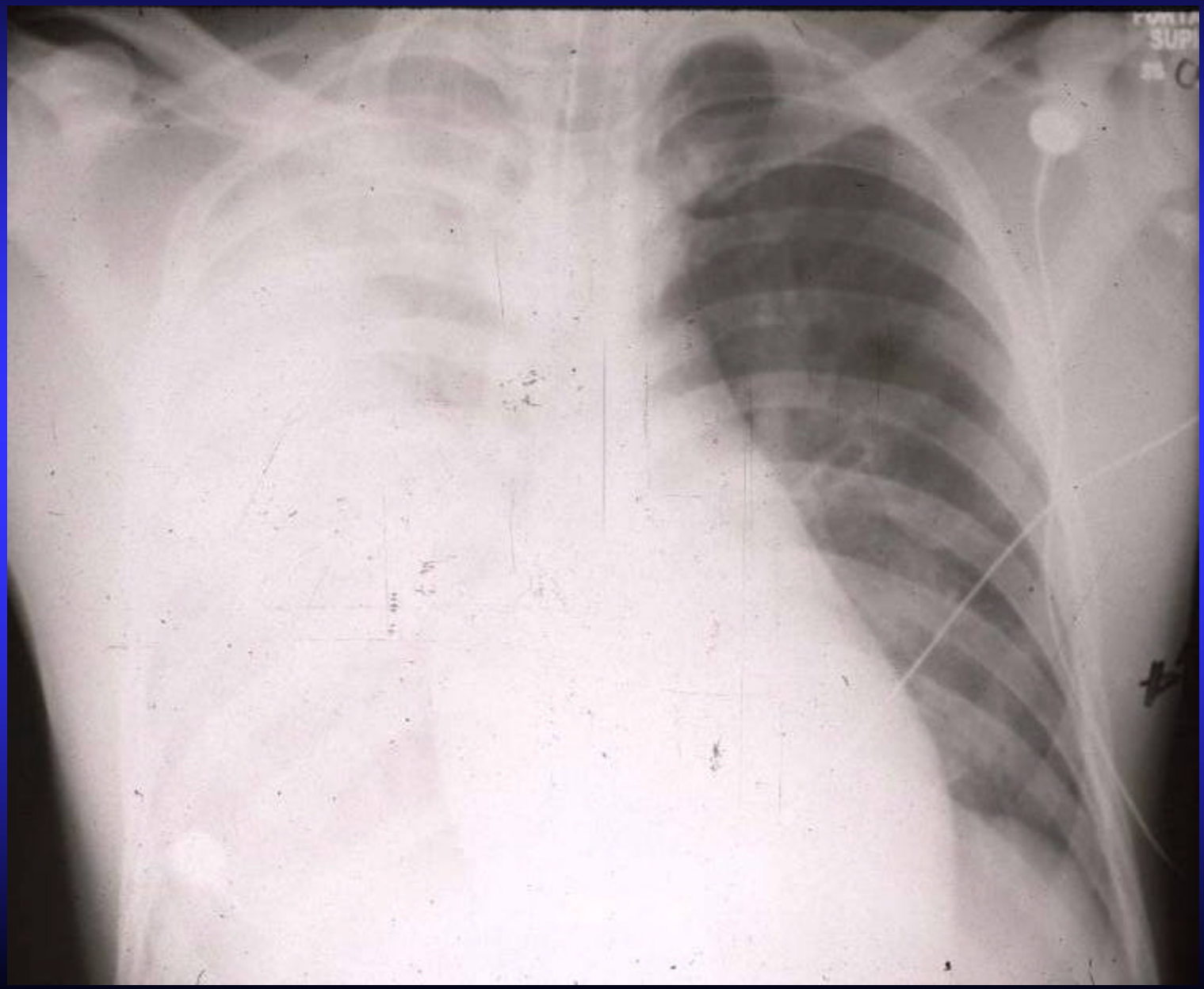
Pneumonic plague epidemics in Manchuria, 1910-11 and 1920-21

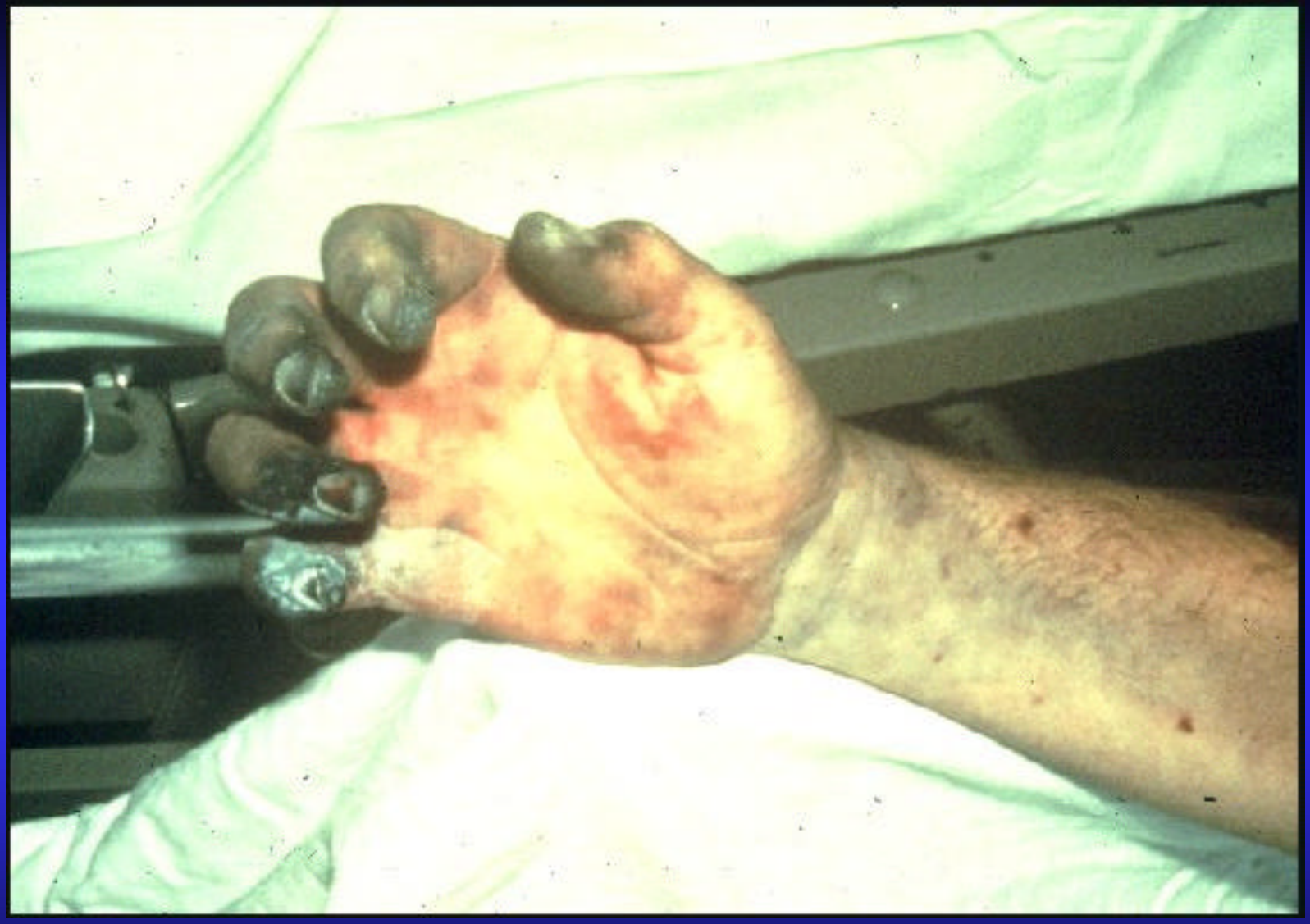


Primary Pneumonic Plague (1)

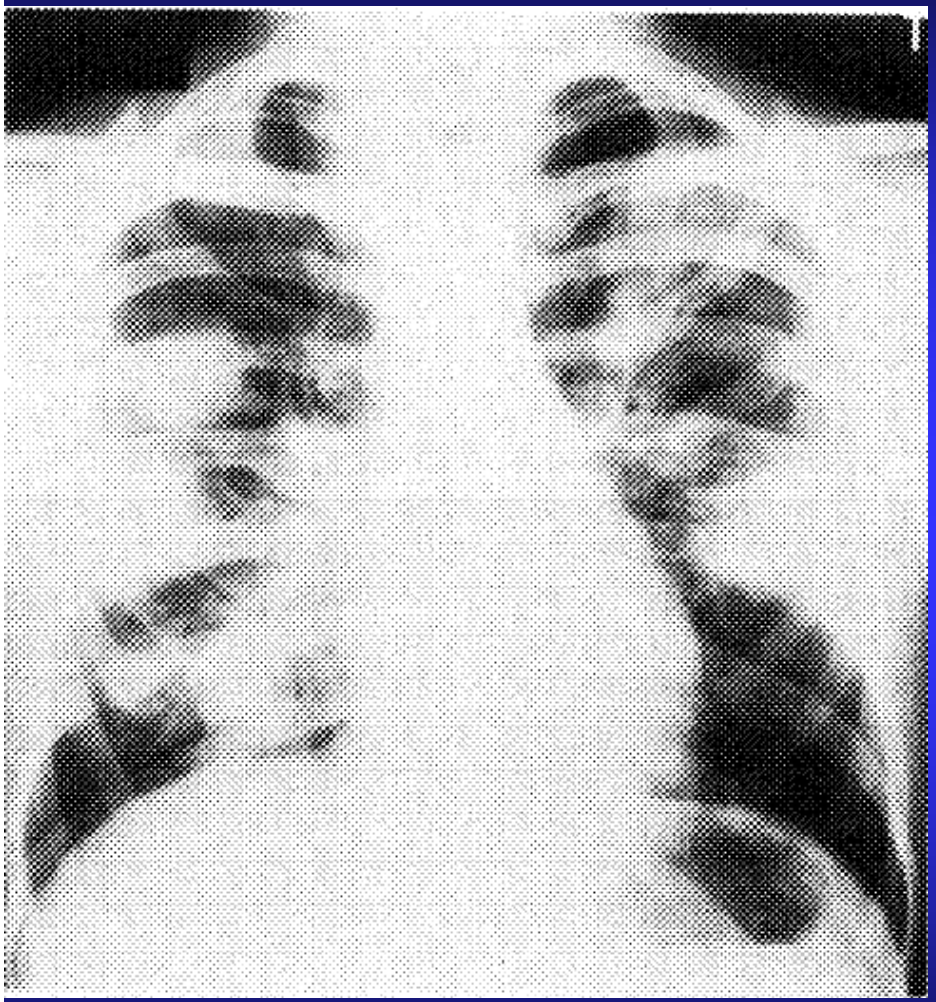


Same case, 12 hours later

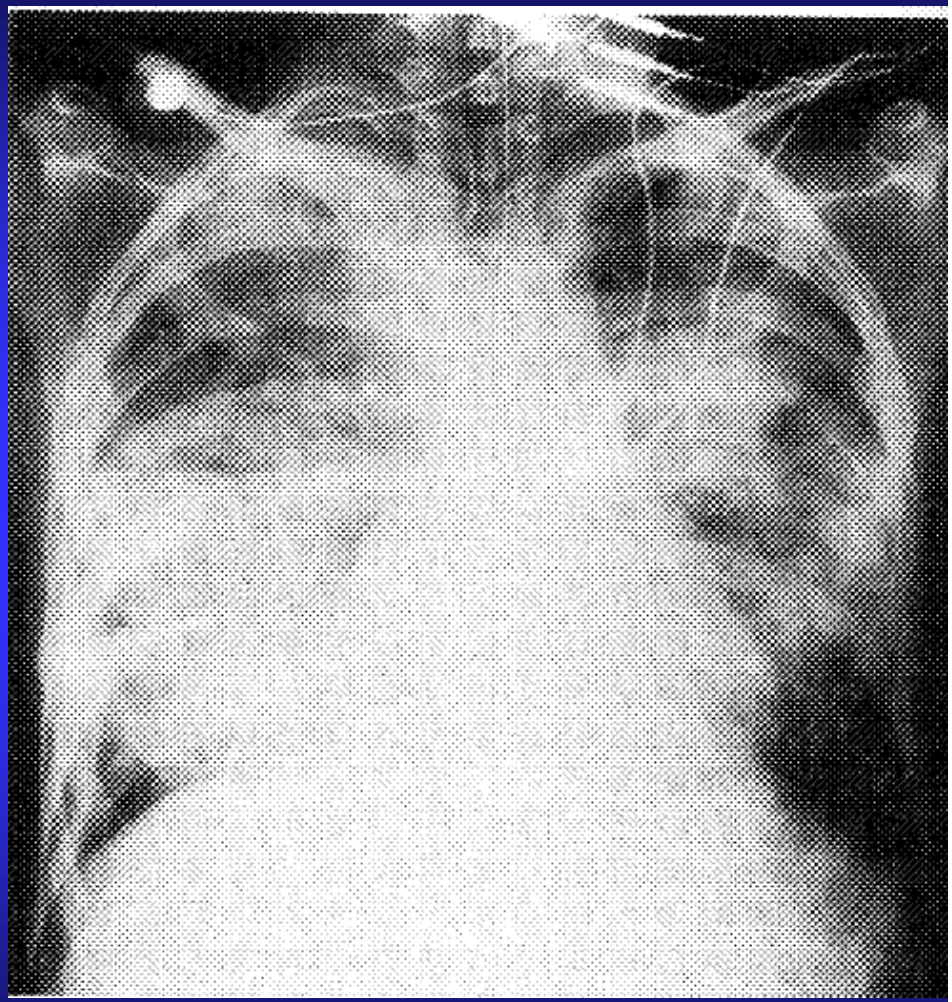




Secondary Pneumonic plague in a 12-yr old boy



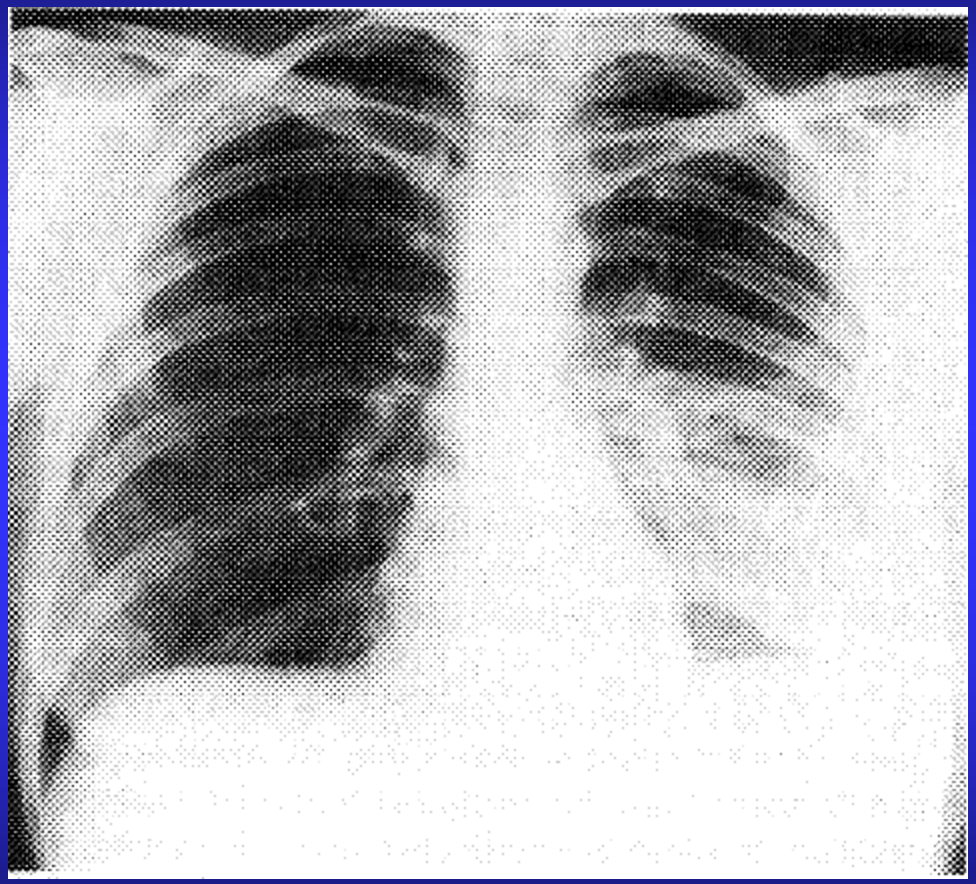
Large nodular densities



12 hours later

Source: Alsofrom DJ, et al. Radiographic manifestations of plague in New Mexico, 1975-1980. Radiology 1981

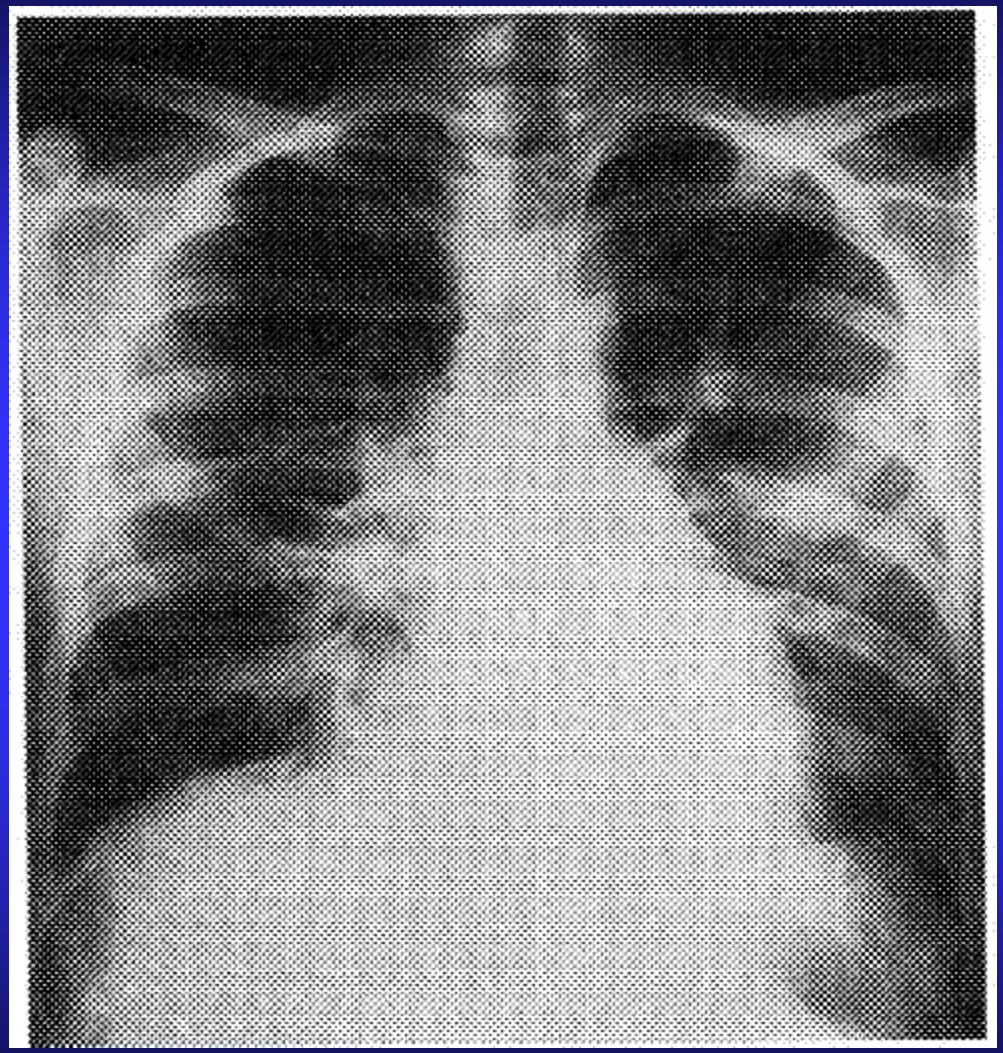
Secondary Pneumonic plague, Patient 2



Left pleural effusion, lower-lobe cavitary lesion

Source: Alsofrom DJ, et al. Radiographic manifestations of plague in New Mexico, 1975-1980. Radiology 1981

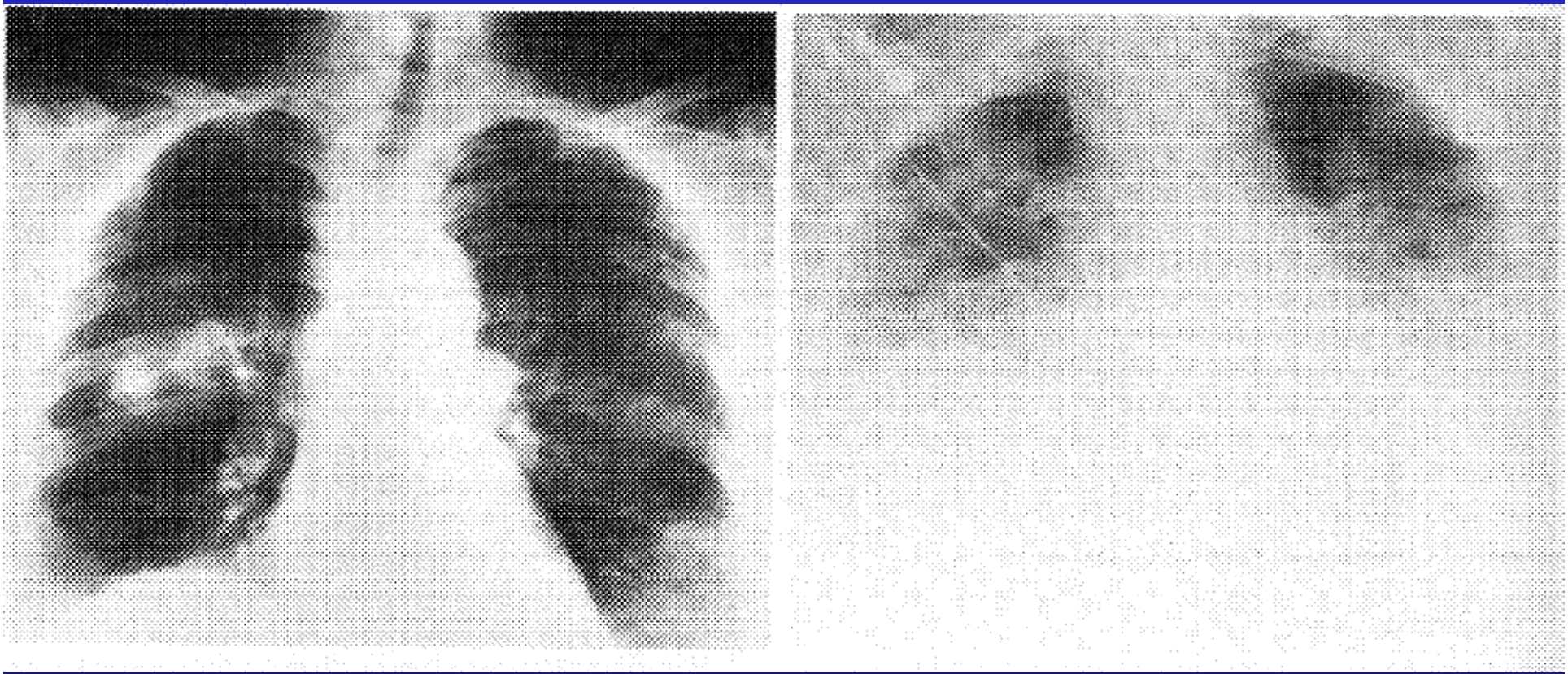
Secondary Pneumonic plague, Patient 3



Bilateral pulmonary parenchymal infiltrates

Source: Alsofrom DJ, et al. Radiographic manifestations of plague in New Mexico, 1975-1980. Radiology 1981

Bubonic plague with DIC; NOT plague pneumonia



Source: Alsofrom DJ, et al. Radiographic manifestations of plague in New Mexico, 1975-1980. Radiology 1981

Treatment of plague

- Parenteral
  - Streptomycin
  - Gentamicin*
  - Doxycycline
  - Ciprofloxacin*
- Oral (mass casualty setting)
  - Doxycycline
  - Ciprofloxacin*
- Post-exposure prophylaxis
  - Trimethoprim-sulfamethoxazole

* Not FDA-approved

Person-to Person Transmission

- Only pneumonic plague is contagious
- Risk not as great as often thought
  - Last case in US in 1924
  - Only close contacts
  - Exposure closer than 2 meters
  - Surgical mask or N-95 protective

- Mainly in later stages, with bloody sputum
- Not after 1-2 days of antimicrobial therapy

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CDC clinical trials

Uganda

Madagascar

Two parts

1. Safety and effectiveness of gentamicin

   P.I.: Jacob Kool

   - Uganda: compare to doxycycline
   - Madagascar: to streptomycin

2. Evaluate new rapid diagnostic tests

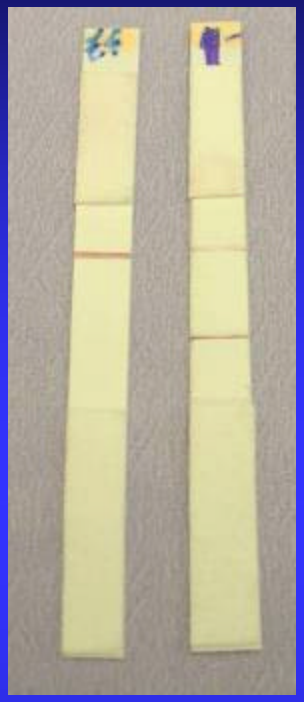
   P.I.: Marty Schriefer

   - 4 brands
   - F1 antigen capture

- Funded by FDA

Rapid diagnostic tests

- Developed in US
- Based on F1 antigen capture
- Approved for non-human use only
- One is already used in Madagascar



Institut Pasteur Madagascar

Critical Reagents Program

Tetracore

New Horizons


Mediterranean Sea
Tunisia
Morocco
Algeria
Libya
Egypt
Western Sahara
Red Sea
Mauritania
Mali
Niger
Chad
Eritrea
Sudan
Arabian Sea
Senegal
Guinea Bissau
Burkina Faso
Djibouti
Guinea
Benin
Nigeria
Somalia
Sierra Leone
Ethiopia
Cote d'Ivoire
Ghana
Togo
Central African Republic
Liberia
Cameroon
Gulf of Guinea
Equatorial Guinea
Uganda
Sao Tome and Principe
Kenya
Gabon
Congo
Rwanda
Congo, DRC
Burundi
Seychelles
Tanzania
Atlantic Ocean
Comoros
Glorioso Islands
Angola
Malawi
Mayotte
Zambia
St. Helena
Mozambique Channel
Mozambique
Zimbabwe
Madagascar
Reunion
Namibia
Botswana
Swaziland
Indian Ocean
South Africa
Lesotho

Logistics

- Renovated & equipped central laboratories
- Field sites:
  - Colorimeters, centrifuges, audiometers
  - Electricity, refrigerators, communications
- Vehicles
- Hired and trained field staff
- IRB approvals
- Accounting

Uganda

Central lab

14 field sites

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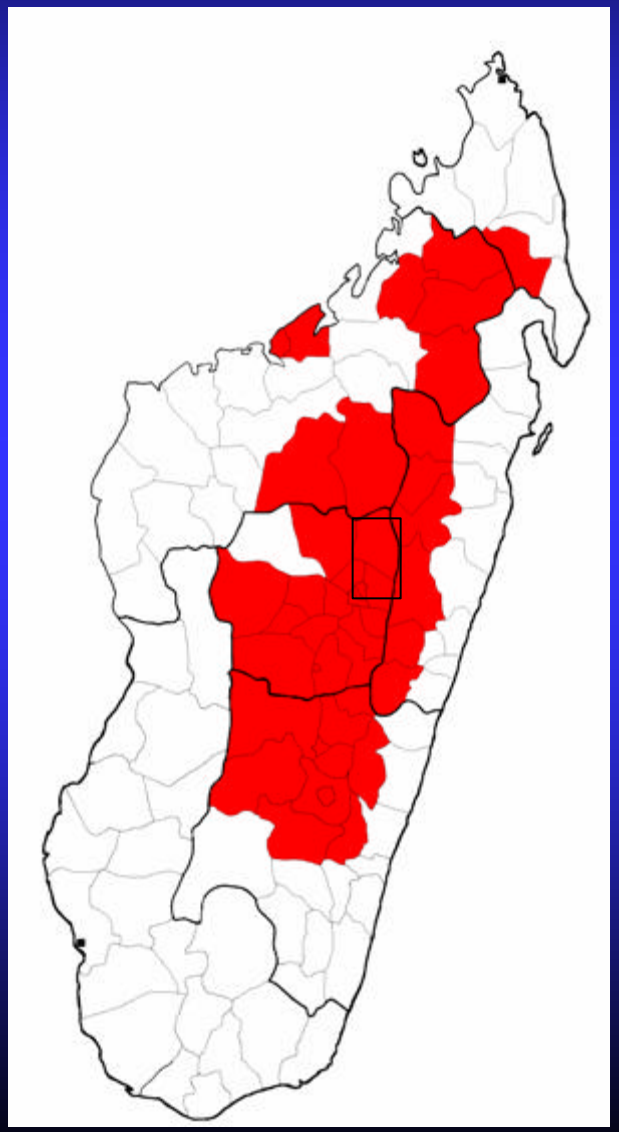
Study sites, Madagascar

- 1 Hospital
- 10 rural clinics



Timeline

- Enrollment started October 2004
- Two seasons
- Project ends spring 2006

- Would like to continue to use sites
  - Novel methods for control ?
  - Fluoroquinolone clinical trial ?
  - Vaccine evaluation ?

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